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PERSPECTIVES

Global transmission of multiple-drug resistant *Neisseria gonorrhoeae* strains refractive to cephalosporin treatment

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Recently, in many countries gonorrhea cases are on the rise. The World Health Organization estimated global annual gonorrhea cases of 62 million in 1999. Gonorrhea infection may increase susceptibility to and transmission of human immunodeficiency virus (HIV). In addition, due to sharing of same transmission route and overlapping risk groups, gonorrhea may serve as a risk marker for infection of HIV and other sexually transmitted infections. In Taiwan, according to Statistics of Communicable Diseases and Surveillance of Taiwan-CDC, 2265 new cases were reported for 2010, with an incidence of 9.79 per 100,000 people.

In only a few decades, *Neisseria gonorrhoeae* has rapidly developed resistance to multiple antibiotics, such as sulfanilamide, penicillins, tetracyclines, and fluoroquinolones. Recently, the third generation cephalosporins, or extended-spectrum cephalosporin (ESC), currently the last remaining treatment options in the drug pipeline, were proposed as alternative antibiotics for treatment of gonorrhea. However, susceptibility to all ESCs (oral and injectable) is decreasing rapidly. Alarmingly, treatment failures with oral ESCs have been reported in many countries. In Taiwan, according to the 2133 isolates (representing 26.7% of the 8,001 reported cases) of gonococci-National Isolate Collection for Epidemiology (G-NICE) surveillance spanning 2008–2011, resistant rates [criteria: European Committee on Antimicrobial Susceptibility Testing (EUCAST) 2011, R: Minimum Inhibitory Concentration (MIC) $\geq$ 0.25 mg/L and Clinical And Laboratory Standards Institute (CLSI) 2011, S: MIC $\leq$ 0.25 mg/L] to the oral cephalosporin, cefixime was 2.63% for MIC $\geq$0.25 mg/L, while for injectable cephalosporin, ceftriaxone was 0% for MIC $\geq$0.25 mg/L. The maximum MIC was 0.5 mg/L and 0.19 mg/L for cefixime and ceftriaxone, respectively (our unpublished G-NICE surveillance data).

Molecular epidemiology study employing molecular typing methods such as *N gonorrhoeae* multiantigen sequence typing (NG-MAST) or serotyping in conjunction with sequencing the *penA* allele encoding penicillin-binding protein 2 and other resistance determinants (*mtrR*, *penB*, *ponA*, and *pilQ*) is helpful in tracing the resistant clones.[1] Recent studies have indicated that most of the gonococcal isolates with decreased susceptibility to the ESC belongs to a few specific major clones. In Taiwan, the majority of cefixime-reduced susceptible strains belong to related clones containing NG-MAST type10 *tbpB* and mosaic types X *penA* allele such as sequence type (ST) 835, 2180, and ST2253. These clones are multidrug resistant (MDR) with a high percentage of resistance rate to penicillin, tetracycline, and ciprofloxacin, and mostly circulate in high-risk homosexual or bisexual sexual networks.[2]

More recently, global rapid spread of ESC-reduced susceptible ST1407 and related STs that share the *tpbB* allele (allele 110), but with different *por* alleles (por 908 related) and harbor mosaic *penA* allele types XXXIV have been reported in Japan[3] and in Europe[4–6], such as England and Wales, Sweden, the Netherlands, Norway,

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and Italy. ST1407 is a successful clone and has Previously been found in the United States, Australia, and many European countries. The threat is imminent with increasing reports on MDR ST1407 strains render ESC treatment failure in many European countries,[7,8] such as France, Sweden, England and Norway.

The emergence of MDR ST1407 with decreased susceptibility to ESCs, such as ST1407, threatens to erode the last remaining effective agents for treatment of gonorrhea. The rapid spread of these clones might be facilitated by high-risk sexual behavior and should be monitored closely to identify potential treatment failure. Increasing frequency of MDR gonococci with reduced susceptibility to ESC especially in some high-risk groups such as men who have sex with men has been noted.[9] Continuous and global concerted surveillanceare paramount to trace the emergence, introduction, and transmission of specific strains as well as the sexual networks they circulate. The finding that these specific clones may transmit across national boundaries and between different sexual networks highlights the need for undertaking intervention as well as risk-reduction consultation in such core-risk groups.[10]

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